

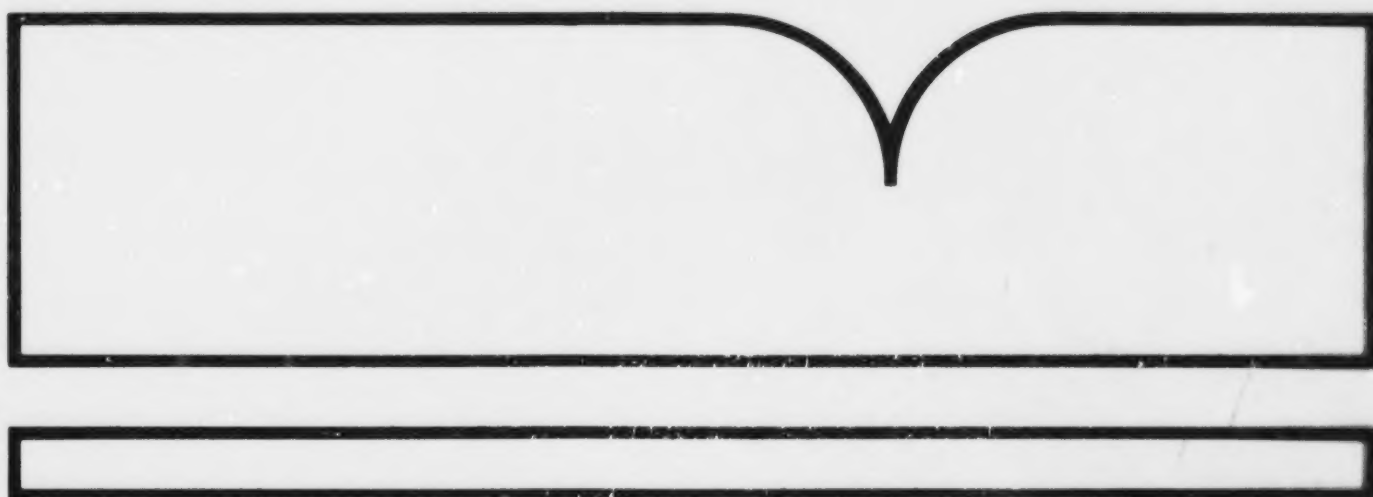
Drinking Water Source and
Risk of Bladder Cancer
A Case-Control Study

(U.S.) National Cancer Inst., Bethesda, MD

Prepared for

Health Effects Research Lab.
Research Triangle Park, NC

Jan 85



U.S. Department of Commerce
National Technical Information Service

NTIS

PB85-156537

EPA/600/D-85/007
January 1985

DRINKING WATER SOURCE AND RISK OF BLADDER
CANCER: A CASE-CONTROL STUDY

by

Kenneth P. Cantor, Robert Hoover,
Patricia Hartge, Thomas J. Mason,
Debra T. Silverman and Lynn I. Levin
Environmental Epidemiology Branch
National Cancer Institute
Bethesda, Maryland 20205

Project Officer

Leland J. McCabe
Toxicology and Microbiology Division
Health Effects Research Laboratory
Cincinnati, Ohio 45268

HEALTH EFFECTS RESEARCH LABORATORY
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
RESEARCH TRIANGLE PARK, NORTH CAROLINA 27711

REPRODUCED BY
NATIONAL TECHNICAL
INFORMATION SERVICE
U.S. DEPARTMENT OF COMMERCE
SPRINGFIELD, VA. 22161

TECHNICAL REPORT DATA (Please read Instructions on the reverse before completing)		
1. REPORT NO. EPA/600/D-85/007	2.	3. RECIPIENT'S ACCESSION NO. PB85 156537 /AS
4. TITLE AND SUBTITLE DRINKING WATER SOURCE AND RISK OF BLADDER CANCER: A CASE-CONTROL STUDY		5. REPORT DATE January 1985
		6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S) K.P. Cantor, R. Hoover, P. Hartge, T.J. Mason, D.T. Silverman & L.I. Levin		8. PERFORMING ORGANIZATION REPORT NO.
9. PERFORMING ORGANIZATION NAME AND ADDRESS Environmental Epidemiology Branch National Cancer Institute Bethesda, MD 20205		10. PROGRAM ELEMENT NO. CBMC1A
		11. CONTRACT/GRANT NO. ---
12. SPONSORING AGENCY NAME AND ADDRESS Health Effects Research Laboratory Office of Research and Development U.S. Environmental Protection Agency Research Triangle Park, North Carolina 27711		13. TYPE OF REPORT AND PERIOD COVERED Proceedings Paper
		14. SPONSORING AGENCY CODE EPA-600/11
15. SUPPLEMENTARY NOTES P.O.: L.J. McCabe, TMD, HERL (CI).		
16. ABSTRACT A water source component was included in a large population based case-control interview study of artificial sweeteners. Relative risk from using chlorinated surface water sources is not elevated in the exposed groups, and there is no suggestion of a duration-response relationship, but an increasing risk of bladder cancer with duration of exposure to chlorinated surface water is observed among persons otherwise at lowest risk and is consistent across the sexes. Geographical differences in bladder cancer risk patterns suggest the possibility of water contaminants in agricultural areas of ground water contaminants in New Jersey.		
17. KEY WORDS AND DOCUMENT ANALYSIS		
a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group
18. DISTRIBUTION STATEMENT Release to Public	19. SECURITY CLASS (This Report) Unclassified 20. SECURITY CLASS (This page) Unclassified	21. NO. OF PAGES 17 22. PRICE

NOTICE

This document has been reviewed in accordance with U.S. Environmental Protection Agency policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

Chlorine reacts with naturally-occurring organic compounds in water treatment plants to produce halogenated byproducts, including chloroform and other trihalomethanes. Among these compounds, chloroform is a carcinogen (1), others are mutagenic in bacterial tester strains (2), and concentrated mixtures of the higher molecular weight organic fractions transform mammalian cells in tissue culture (3) and induce skin-painted tumors in rodents (4). This raises the possibility that the time-tested benefits of chlorine to control infectious disease may be, in part, offset by increased cancer risk in continuously exposed populations.

Some drinking water supplies are also contaminated by other potentially toxic agents from industrial or municipal outfalls, agricultural and municipal runoff, or toxic waste dumps. While organic chemicals such as trichloroethylene, benzene, or perchloroethylene and cations such as cadmium or arsenic pose important public health threats to some exposed populations, affected water supplies are usually limited geographically and temporally. This does not minimize the threat posed by such contaminants in some local water supplies, nor the threat of future problems in many others. In contrast, chlorination byproducts have been widespread and their historical distribution patterns can be deduced from knowledge of water sources and disinfection practices used in the past.

Several epidemiologic studies have evaluated the possibility of a link between drinking water contaminants and cancer in human populations. The first studies were ecologic in design. More recent work used a case-control approach based on death certificates. Many of these studies linked bladder cancer mortality with exposure indicators - water source type and treatment - that were used as surrogates of contaminant levels (5, 6, 7). Among these surrogate measures are surface (as contrasted with ground) source, chlorinated (as compared with non-chlorinated) source, and recent measures of chloroform

concentration. To further pursue these observations, we incorporated a water source component in a large population-based case-control interview study of bladder cancer designed at the National Cancer Institute in 1977.

Eligible cases included all persons aged 21-84 diagnosed with cancer of the urinary bladder in 1978 and resident in 10 areas of the United States; the states of Connecticut, Iowa, New Jersey, New Mexico, and Utah, and metropolitan Atlanta, Detroit, New Orleans, San Francisco, and Seattle. Slightly less than a third of the cases were from New Jersey. Connecticut, Iowa, Detroit and San Francisco each accounted for more than ten percent. Bladder cancer is primarily a disease of older men. There were 3 times as many men as women cases and the median age was 67. A total of 2982 cases, 73% of the eligible pool, were interviewed. Controls were randomly selected from the population of each area, frequency matching on sex, 5-year age group, and study area. Controls aged 21-64 years were selected by a random-digit dialing method, and controls 65-84 years of age randomly from a roster provided by the Health Care Financing Agency. Five thousand seven hundred eighty-two population-based controls were interviewed. Details on the study design and methods are published elsewhere (8).

Cases and controls were interviewed at home by trained interviewers. Items on the questionnaire included demographic background; a smoking, occupational, and medical history; artificial sweetener use; and other factors possibly linked to bladder cancer, including hair dyes, coffee and tea consumption, and fluid ingestion. Each respondent was also asked to name each city or town in which he or she had lived for a year or more, the years moved into and out of that place, and whether the primary source of drinking water at each place was a private well, the community water supply, bottled water, or another source. We coded geographic areas by a standard coding scheme (9).

In collaboration with the Cincinnati Health Effects Research Laboratory of the Environmental Protection Agency, we independently surveyed all community water supplies that served more than 1000 persons in the 10 study areas. We collected historical information on water source, treatment, and geographic distribution since 1900. Water sources were classified as surface or ground, and further details on source characteristics and potential contamination were recorded. Treatment information, especially chlorination, was also gathered. Although details on amounts of added chlorine were often lacking, we were able to ascertain the years in which chlorination disinfection had been used. The town and cities historically served by each water source were listed and coded with the same geocoding scheme used for residential histories.

A year by year record of water source and treatment was created for each study respondent. For each year that a respondent lived in one of the 10 study areas and used a community supply, we looked up water source and treatment information in the water supply data file. We were not able to describe water source for years when respondents used community sources outside of the study areas or when they lived in very small communities with supplies not covered by our survey.

Of the 587,565 person-years lived by all respondents since 1900, 444,735 (76%) were at a known water source. This ranged from 63% in New Mexico to 83% in Iowa. The year by year profile of water source and treatment information for each person provided us with a flexible tool to look at patterns of water use in the study population as well as to define individual exposures.

We have estimated relative risk according to several different measures derived from drinking water histories. Here we report on risk as related to

the number of years that a respondent lived at a residence served by a chlorinated surface source. Most chlorinated surface sources have much higher levels of chlorination byproducts than most chlorinated or non-chlorinated ground water sources (10) so duration of exposure is a crude index of dose.

We used the odds ratio to estimate the relative risk. Logistic regression for unmatched data was used to obtain maximum likelihood point and 95% confidence interval estimates of the odds ratio and to control for the potential confounding effects of selected variables (11, 12). Among the potential confounders in most calculations were geographic area (10 levels), 6 levels of cigarette smoking intensity, 3 age groups, a 1/0 variable for usual employment as a farmer, and race and sex when the analyses were not race- or sex-specific.

Table 1 shows the overall relative risk among whites by the number of years at a chlorinated surface water source. All risks are relative to those who lived at places never served by such sources. Compared to this baseline measure are respondents with less than 20 years, 20 to 39, 40 to 59 years, and 60 or more years at places with chlorinated surface sources. Relative risk is not elevated in the exposed groups, and there is no suggestion of a duration-response relationship.

Eligibility for inclusion in the analyses reported here was restricted in two major ways. 1) Preliminary analyses suggested a potential for confounding of drinking water associations by employment in a high risk occupation for bladder cancer (as identified by D. Silverman, L. Levin, and R. Hoover at NCI). To control for this, we included only persons who never held a high risk job. 2) Among some persons in "low exposure" categories, (i.e. those with few years known to be served by a chlorinated surface source), there was uncertainty as to exposures during years they were not known to be served by a chlorinated

surface source. Some of these years were classified as "municipal, not otherwise specified", or "unknown", and in such cases assignment to a more precise exposure category was not possible. We wished to remove from the analysis those persons whose exposures were least certain. In addition, we desired to maximize the number of "non-exposed" years spent at non-chlorinated ground sources (low exposure) while still including enough subjects to maintain adequate statistical power. To these ends, we further reduced the analysis population to those whose years at a chlorinated surface source plus years at a non-chlorinated ground source summed up to at least half of their lifetime.

Interesting differences in relative risk for duration of exposure to chlorinated surface waters are observed within geographic regions (Table 2). Elevated relative risks are seen in New Mexico, Utah, and Iowa with the number of years resident at a place served by a chlorinated surface source. The number of respondents in New Mexico and Utah is small, but the result is statistically significant. The pattern in Iowa is also interesting, and is apparent among smokers and non-smokers. It may be important that these three areas are the most intensely agricultural of the study areas. In New Jersey, the overall relative risk was less than 1.0, and risk decreased with the number of years that a chlorinated surface source was used. We cannot explain this observation by confounding by other risk factors for bladder cancer that we have evaluated. Associations of bladder cancer with contaminated ground water in New Jersey is one issue that deserves exploration.

Table 3 shows results of analysis by major smoking category - non-smokers, former smokers, and current smokers. Among non-smokers, the relative risk generally increases with the number of years at a residence with a chlorinated surface source. The relative risk among those with the longest exposure-60 or more years - is 2.3, and the increase is statistically significant. Former smokers show an uneven risk pattern, and the risk among current smokers appears

to vary inversely with the number of years exposed. The unusual and unexpected inverse risk pattern among current smokers could not be explained by confounding by smoking level within broad smoking category or by several other factors that we investigated, including age. Among non-smokers, there are similar risk patterns for each sex, with the relative risk increasing with the number of years at a surface source, rising to 2.2 in men and 2.5 in women in the longest exposure category. Former smokers show divergent patterns for the sexes. Current smokers of both sexes show inverse risk patterns with number of years exposed.

When evaluating these results, some limitations must be considered. The study had its origins in the issue of saccharin as a human bladder carcinogen, and therefore study areas were not selected with the water source hypothesis in mind (13). Some of the places, notably the five metropolitan areas, are predominantly served by one water source. This limits intraregional variability of exposure in some areas and dampens the statistical power of our large numbers. The exposure measure used here simplifies a complex world by dichotomizing water sources into 'chlorinated surface' and 'non-chlorinated ground'. While based on extensive environmental information, this classification ignores other differences among sources, and may completely misclassify exposure in places with contaminated ground water.

Detection of the relatively small risk differences expected in environmental epidemiologic studies is a challenging task, and great care must be taken to minimize bias and account for risk factors that may confound the result (14). Given the stringent study design and its careful execution, it is unlikely that bias from case or control selection, or from differentially conducted interviews of cases and controls, has influenced our findings (8). Information on factors that remain unknown or that are now thought to possibly

influence bladder cancer risk were not available and could have confounded the results. Although unlikely, confounding could occur if drinking water source is correlated with ingestion of beta-carotene, retinol, or other micronutrients that may behave as tumor promoters or anti-carcinogens.

Our overall finding is of no overall elevation in bladder cancer risk among persons who have lived at places with chlorinated surface water as compared with non-chlorinated ground water, and no dose-response is observed. Among the 10 study areas, respondents from 3 places with agricultural land use show elevated risk for bladder cancer with number of years at a surface source. This is in contrast with decreased risk in the largest study area, New Jersey.

Cigarette smoking is a well known bladder cancer risk factor (15). Among smokers, there is an unexplained negative association with number of years at a chlorinated surface source that is consistent in the sexes. The pattern among former smokers is variable. Among non-smokers who never were employed in a high-risk occupation - a group otherwise at low risk for bladder cancer - the risk is elevated among those served by chlorinated surface sources; there is a duration-response relationship; and the pattern is similar in men and women.

While the overall result is reassuring, these findings raise questions that warrant further elaboration. Although smokers within each water exposure category are at higher risk for bladder cancer than non-smokers, the risk of bladder cancer among smokers with lifetime exposure to non-chlorinated ground water appears to be higher than that among smokers with chlorinated surface drinking water. Whether this is due to confounding by unmeasured risk factors, chance or biological interaction is not currently understood. Geographical differences in bladder cancer risk patterns suggest the possibility of water

contaminants in agricultural areas or ground water contaminants in New Jersey. An increasing risk of bladder cancer with duration of exposure to chlorinated surface water is observed among persons otherwise at lowest risk and is consistent across the sexes. An analytic study with limited statistical power has also noted positive associations of bladder cancer risk with use of chlorinated surface water sources (16). A causal interpretation of these findings would be strengthened by similar observations in another setting.

The information described in this article has been sponsored wholly or in part by the United States Environmental Protection Agency. It has been subject to the Agency's review and has been approved for publication as an EPA document. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

REFERENCES

1. Page, N.P., and Saffiotti, U. Report on Carcinogenesis Bioassay of Chloroform. National Cancer Institute, Division of Cancer Cause and Prevention, Bethesda, MD, 1976.
2. Loper, J.C. Mutagenic effects of organic compounds in drinking water. *Mutat. Res.; Reviews in Genetic Toxicology* 76: 241-268 (1980).
3. Land, D.R., Kurzepa, H., Cole, M.S., Loper, J.C. Malignant transformation of BALB/3T3 cells by residue organic mixtures from drinking water. *J. Environ. Pathol. Toxicol.* 4: 41-54 (1980).
4. Robinson, M., Glass, J.W., Cmehil, D., Bull, R.J., Orthoefer, J.G. Initiating and promoting activity of chemicals isolated from drinking waters in the SENCAR mouse - a five city survey. In *Short-Term Bioassays in the Analysis of Complex Environmental Mixtures, II* (Environmental Science Research, Vol. 22), M.D. Waters et al. (Eds.), Plenum Press, New York, 1980, pp. 177-188.
5. National Academy of Sciences-National Research Council Assembly of Life Sciences. *Drinking Water and Health, Vol. III*, National Academy of Sciences, Washington, D.C., 1980.
6. Wilkins, J.R., III, Reiches, N.A., and Kruse, C.W. Organic chemicals in drinking water and cancer. *Am. J. Epidemiol.* 110: 420-448 (1979).
7. Crump, K.S., Guess, H.A. Drinking water and cancer: Review recent of epidemiological findings and assessment of risks. *Ann. Rev. Public Health* 3: 339-57 (1982).
8. Hartge, P., Cahill, J.I., West, D., Hauck, M., Austin, D., Silverman, D., and Hoover, R. Design and methods in a multi-center case-control interview study. *Am. J. Public Health*, 74: 52-56 (1984).
9. U.S. General Service Administration, Office of Finance, Worldwide Geographic Location Codes. Washington, D.C. U.S. Government Printing Office, 1981.
10. Symons, J.M., Bellar, T.A., Caiswell, J.K. et al. National Organics Reconnaissance Survey for Halogenated Organics. *J. Amer. Water Works Assoc.* 667: 634-647 (1975).
11. Breslow, N.E., Day, N.E. *Statistical Methods in Cancer Research: Vol. I. The Analysis of Case-Control Studies.* Lyon, IARC, Sci. Publ. Issue 32, 338 pp., 1980.
12. SAS Institute. *SAS User's Guide: Statistics.* Cary, N.C. SAS Institute 1982: 257-286.
13. Hoover, R.N., Strasser, P.H. et al. Artificial sweeteners and human bladder cancer. *Lancet* 1: 837-840 (1980).

14. Cantor, K.P. Epidemiologic studies to estimate effects of low-level exposures. In Vouk, V.B. et al., Eds. Methods of Estimating Risk of Chemical Injury: Human and Non-human Biota and Ecosystems. Wiley & Sons. Geneva 1984, pp. 303-325.
15. Matanoski, G.M., Elliott, E.A. Bladder cancer epidemiology. Epidemiol. Rev. 3: 203-229 (1981).
16. Wilkins, J.R., Comstock, G.W. Source of drinking water at home and site-specific cancer incidence in Washington County, Maryland. Am. J. Epidemiol. 114: 178-90 (1981).

Table 1. Relative risks (RR) and 95 percent confidence intervals (95% CI) for bladder cancer according to number of years at a residence served by a chlorinated surface drinking water source.*

YEARS	RR (95% CI)	Number
		(cases, controls)
0	1.0	(231,570)
1-19	1.1 (.8-1.4)	(141,285)
20-39	1.0 (.8-1.3)	(324,650)
40-59	1.0 (.8-1.3)	(437,849)
60+	1.1 (.8-1.5)	(111,196)

*Whites, from logistic regression adjusted for study area (10 strata), sex, age (3 strata), smoking level (6 strata), and usual employment as a farmer (2 strata).

Table 2. Relative risks (RR) and 95 percent confidence intervals (95% CI) for bladder cancer, according to number of years at a residence served by a chlorinated surface drinking water source, by study area.

YEARS	San Francisco/Seattle		New Mexico/Utah		New Orleans/Atlanta	
	RR (95% CI)	Number (cases, controls)	RR (95% CI)	Number (cases, controls)	RR (95% CI)	Number (cases, controls)
0	1.0	(20, 26)	1.0	(15, 75)	1.0	(5, 8)
1-19	0.7 (0.3-2.0)	(16, 37)	4.5 (1.03-19.5)	(6, 8)	0.2 (.03-1.1)	(5, 23)
20+	1.05 (0.4-2.7)	(163, 332)	11.8 (2.5-55.1)	(8, 5)	0.4 (0.1-1.9)	(70, 156)
	Iowa		Detroit		Connecticut	
	RR (95% CI)	Number (cases, controls)	RR (95% CI)	Number (cases, controls)	RR (95% CI)	Number (cases, controls)
0	1.0	(111, 323)	1.0	(6, 9)	1.0	(17, 53)
1-19	1.04 (0.6-1.8)	(26, 64)	1.4 (0.4-5.4)	(12, 15)	1.7 (0.8-3.4)	(36, 64)
20+	1.6 (0.94-2.7)	(35, 55)	1.2 (0.4-3.6)	(197, 278)	1.17 (0.7-2.1)	(158, 378)
YEARS	New Jersey					
0	1.0	(57, 76)				
1-19	0.7 (0.4-1.3)	(40, 76)				
20+	0.7 (0.5-1.1)	(241, 491)				

*Whites, from logistic regression adjusted for sex, age (3 strata), smoking level (6 strata), and usual employment as a farmer (2 strata).

Table 3. Relative risks (RR) and 95 percent confidence intervals (95% CI) for bladder cancer according to number of years at a residence served by a chlorinated surface drinking water source, by cigarette smoking status.

YEARS	NEVER SMOKED		PAST SMOKERS		CURRENT SMOKERS	
	RR (95% CI)	Number (cases,controls)	RR (95% CI)	Number (cases,controls)	RR (95% CI)	Number (cases,controls)
0	1.0	(61,268)	1.0	(83,193)	1.0	(87,109)
1-19	1.3 (.7-2.2)	(29,110)	1.0 (.7-1.7)	(49,104)	0.9 (.6-1.5)	(63,71)
20-39	1.5 (.9-2.4)	(73,236)	1.1 (.7-1.8)	(115,228)	0.7 (.4-1.1)	(136,186)
40-59	1.4 (.9-2.3)	(108,348)	1.2 (.8-1.8)	(163,290)	0.7 (.5-1.2)	(166,211)
60+	2.3 (1.3-4.2)	(46,77)	0.8 (.5-1.5)	(38,82)	0.6 (.3-1.2)	(27,37)

*Whites, from logistic regression adjusted for study area (10 strata), sex, age (3 strata), usual employment as a farmer (2 strata), and (for past smokers), 2 smoking levels, or (for current smokers), 3 smoking levels.